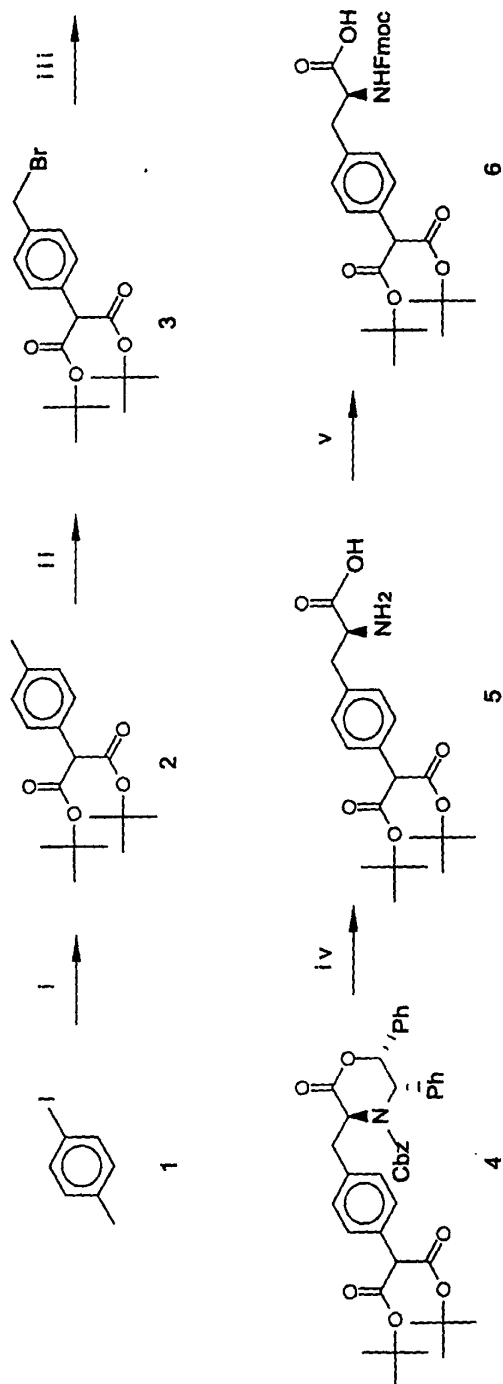
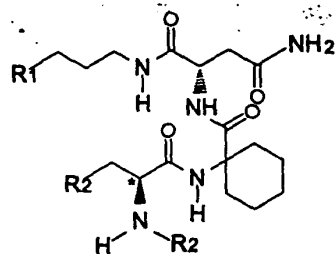


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i. Di-tert-butyl malonate, NaH, CuBr, Dioxane, HMPA, 101°C, 55.2%; ii. NBS, 83.2%;
 iii. Benzyl (2R, 3S)-(-)-6-oxo-2, 3-diphenyl-4-morpholine, LiHMDS, THF, -78°C-R.T., 39.2%;
 iv, H₂, Pd black, 86.3%; v. Fmoc-OSu, Dioxane-H₂O, NaHCO₃, 30-35°C, 50.7%.

FIG. 1



General Structure
(*D, L and racemate claimed)

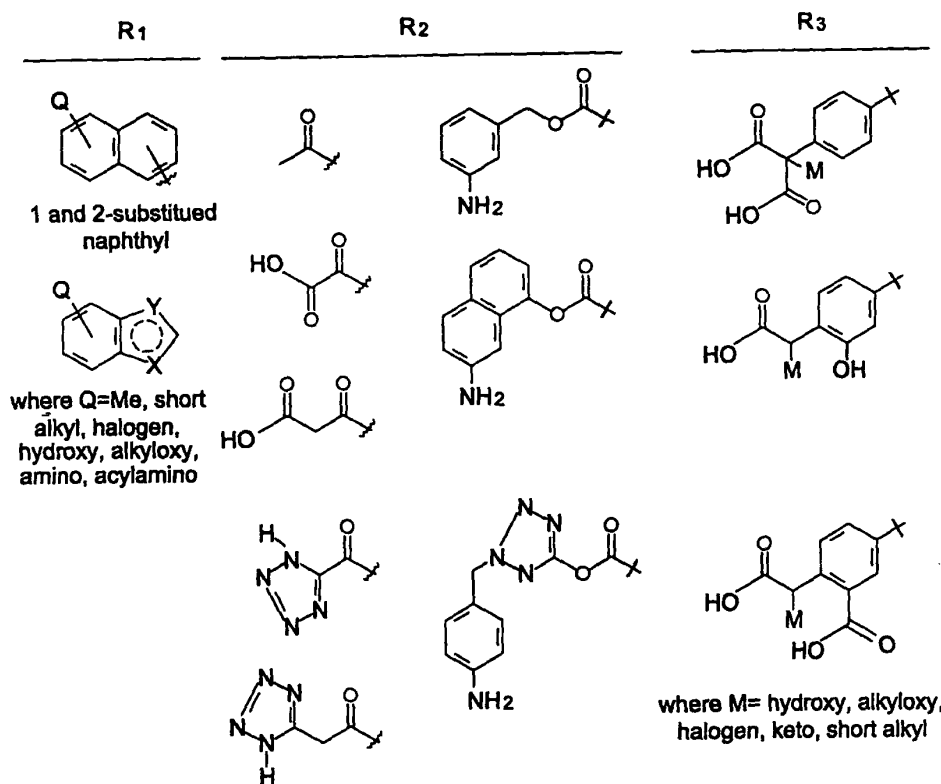
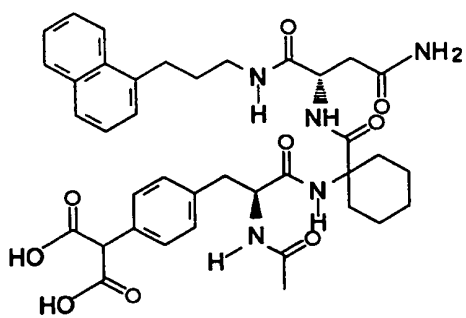
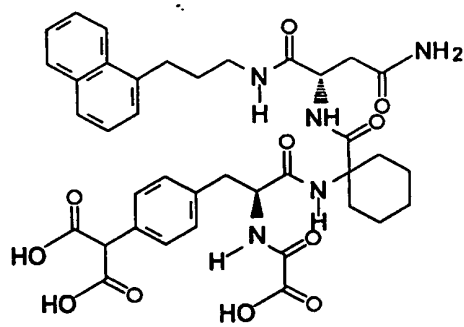


FIG. 2

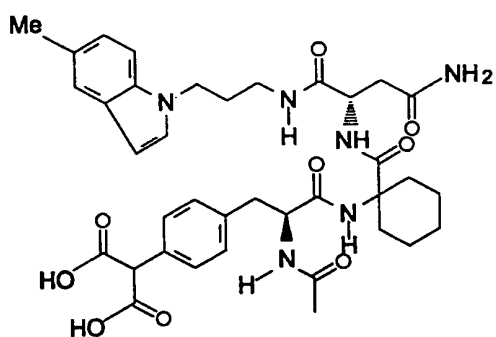
209220-05T/EE660



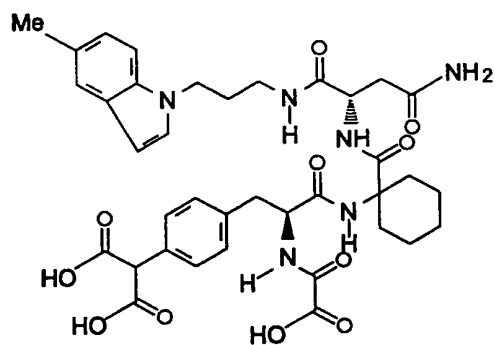
12



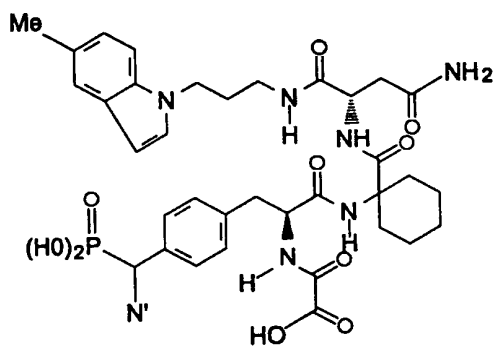
11



18



19

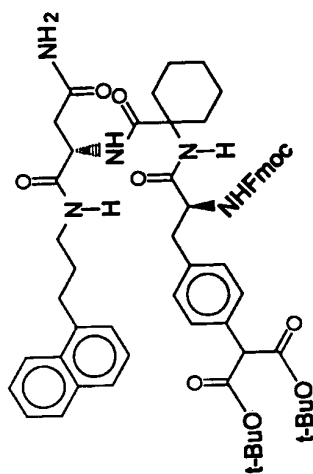


N'=H, halogen, hydroxy, F₂

20(a, b, c, d)

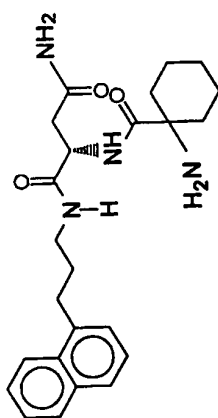
FIG. 3

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8

106C-56-2, HOBt
DIPCDI, DMF, 100%



7

FIG. 4

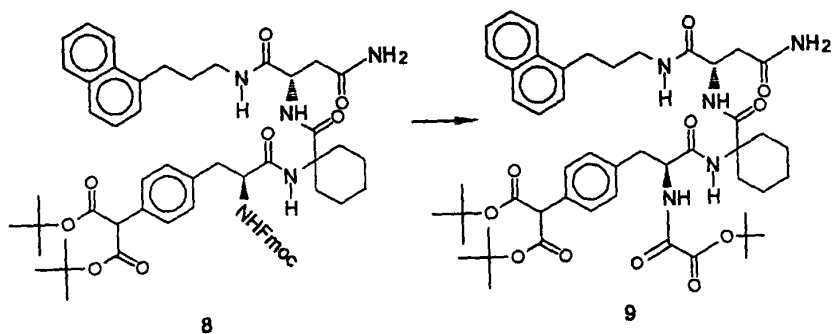


FIG. 5

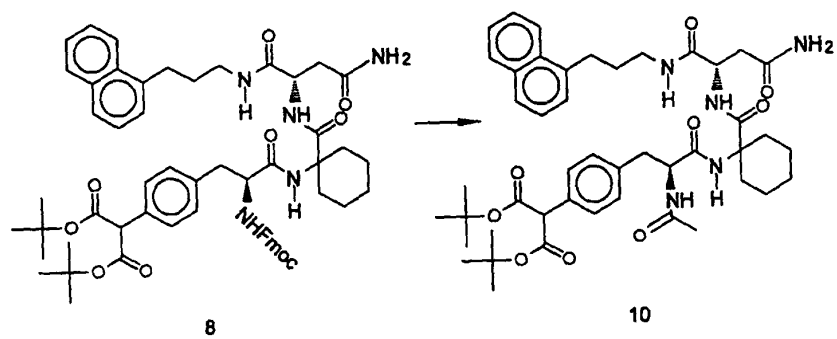


FIG. 6

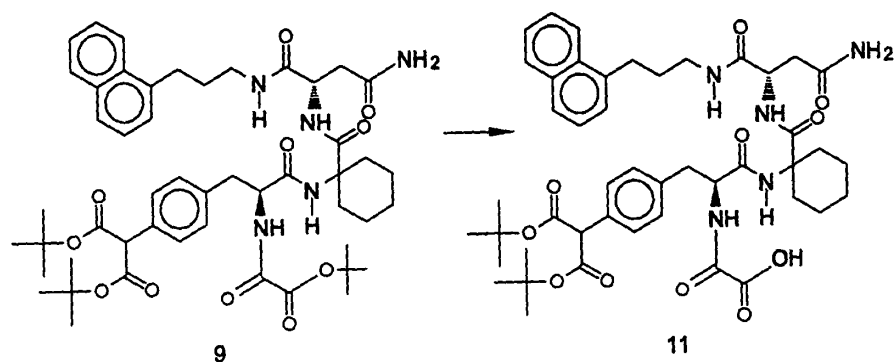


FIG. 7

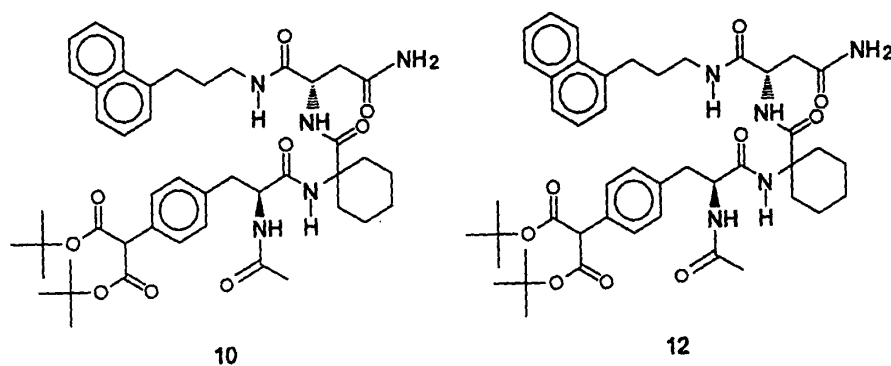


FIG. 8

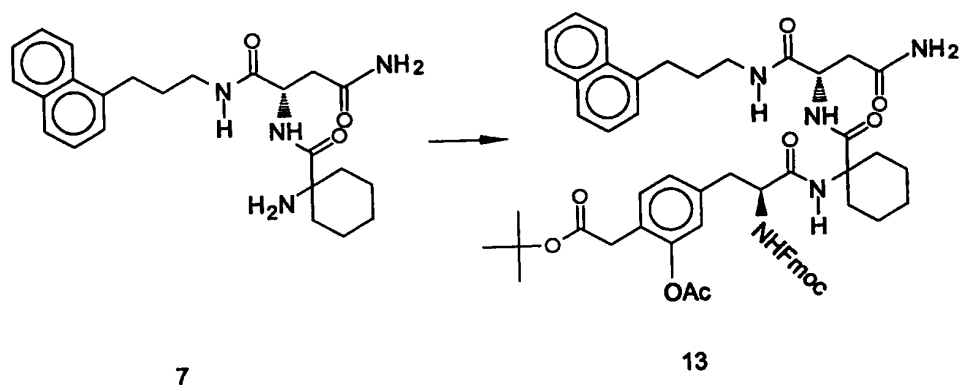


FIG. 9

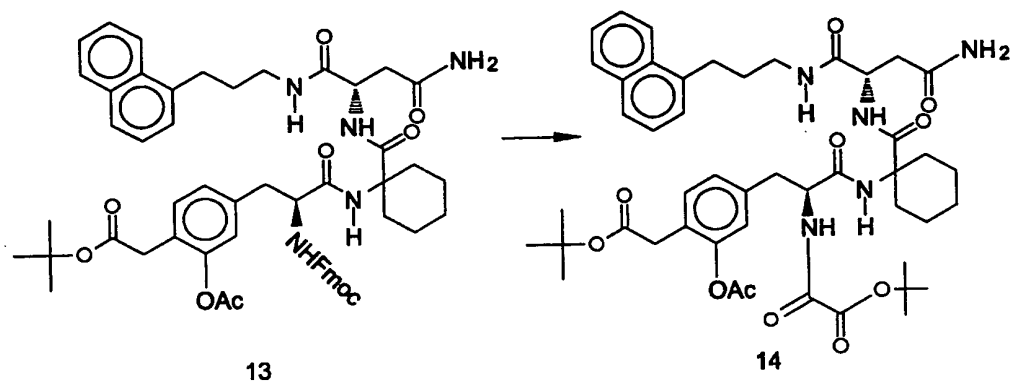


FIG. 10

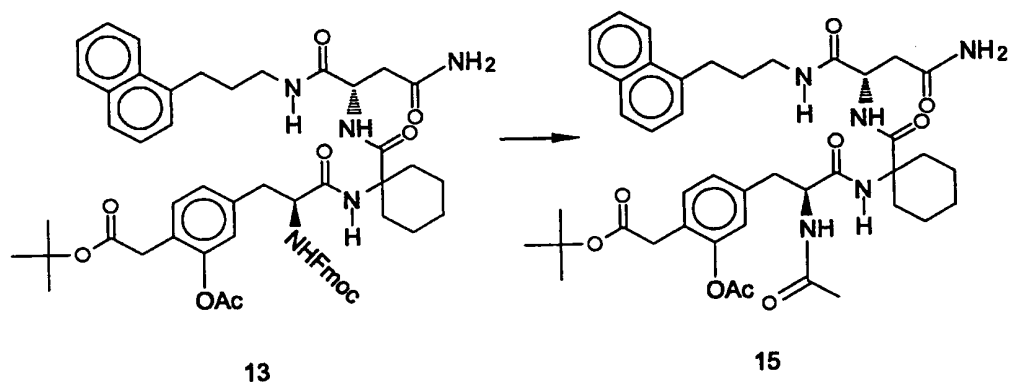


FIG. 11

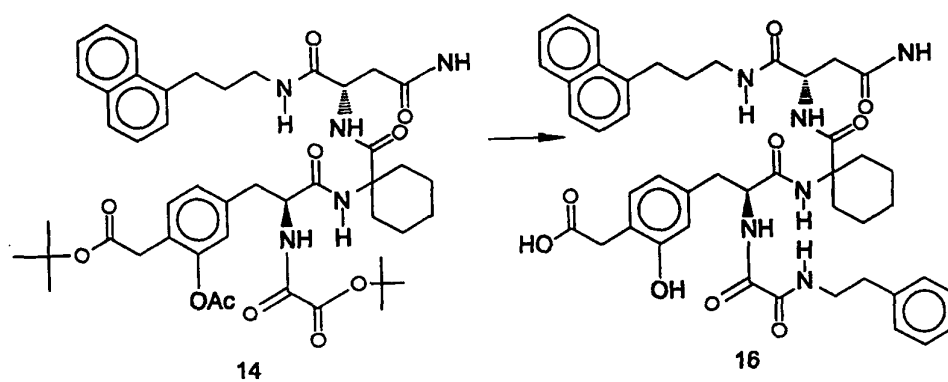


FIG. 12

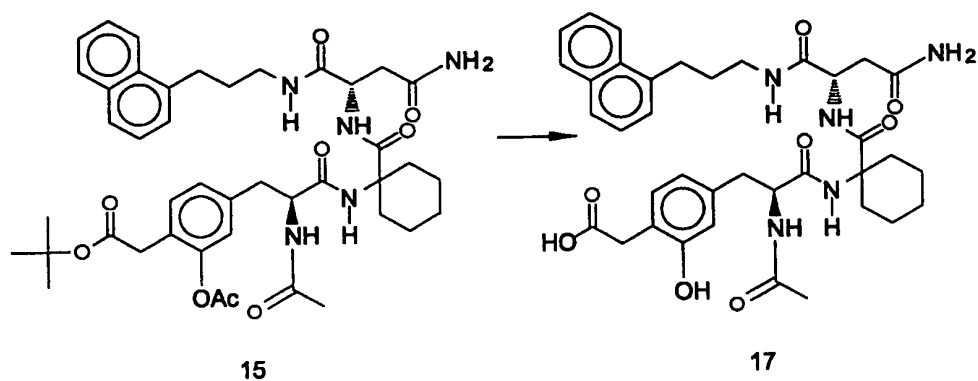
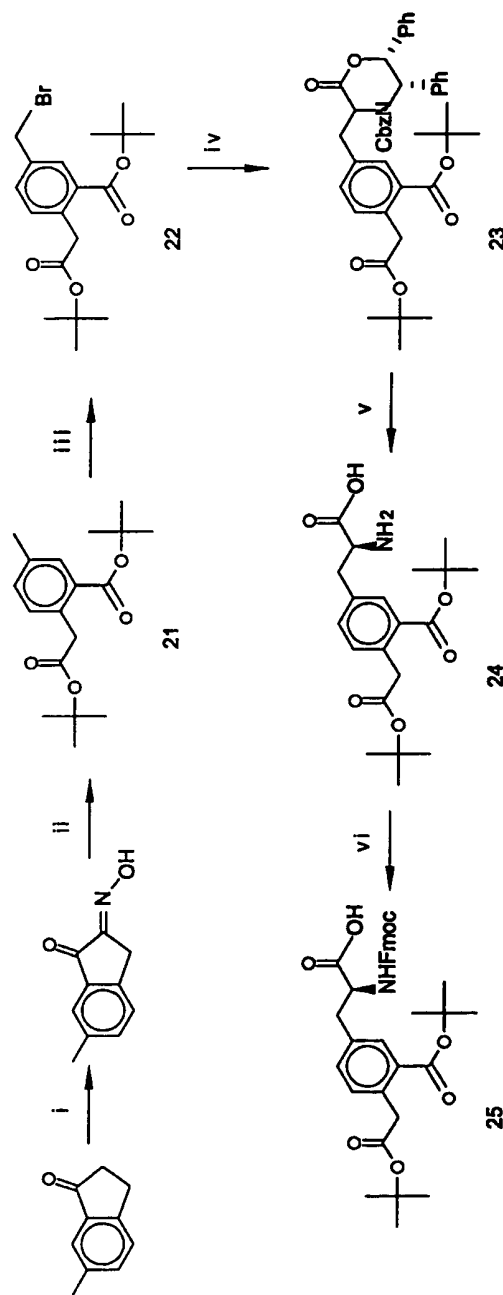


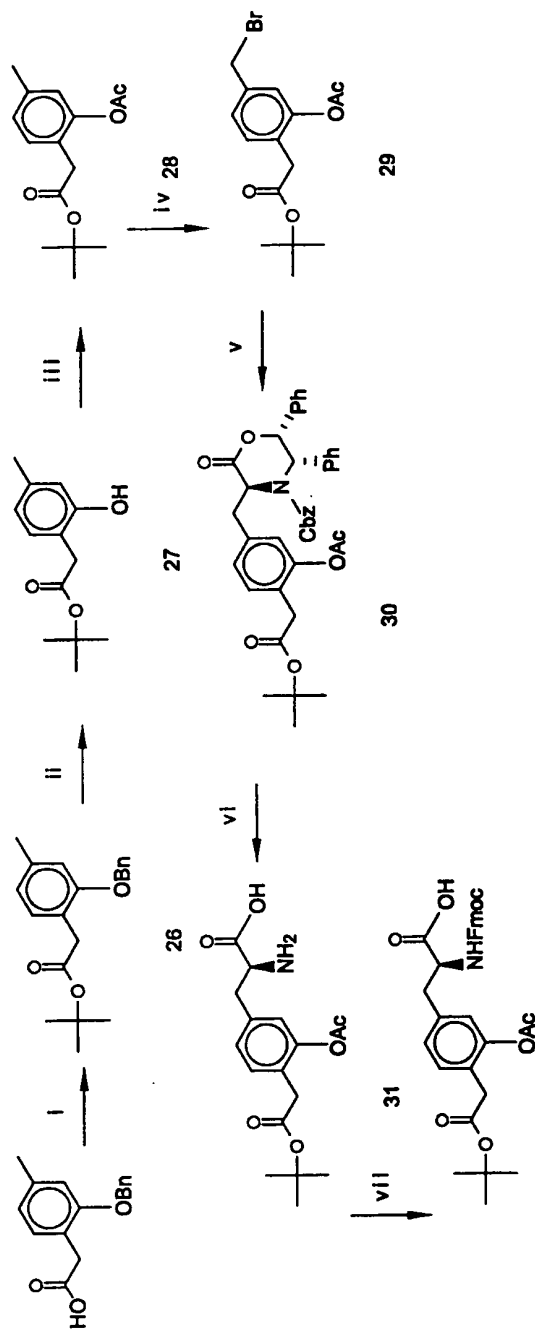
FIG. 13

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- i). Isopentyl nitrite, concd. HCl, 82.5%; ii). a. PCl₃, anhyd. ether, b. NaOH-H₂O, 89.4%
 iii). 2,2,2-trichloroacetamide (t-butyl). BBr₃, CH₂Cl₂-cyclohexane, 83.3%;
 iv. William's reagent, LiHMDS, HMPA, THF, 68.7%; v. H₂, Pd Black, EtOH-THF, 56.6%
 vi. Fmoc-OSu, NaHCO₃, Dioxane-H₂O, 78.4%

FIG. 14



- i). 1. (COCl)₂, 2. t-Butanol, 92.8%; ii). H₂, Pd black, EtOH, 100%; iii). Ac₂O, Pyr., 94%;
 iv). NBS (BzO)₂, 38.8%; v). Williamson's reagent. LiHMDS, THF, -78°C-R.T., 50.5%;
 vi) H₂, Pd Black, EtOH-THF, 100%; vii). Fmoc-Osu, NaHCO₃, Dioxane-H₂O, 39.5%

FIG. 15

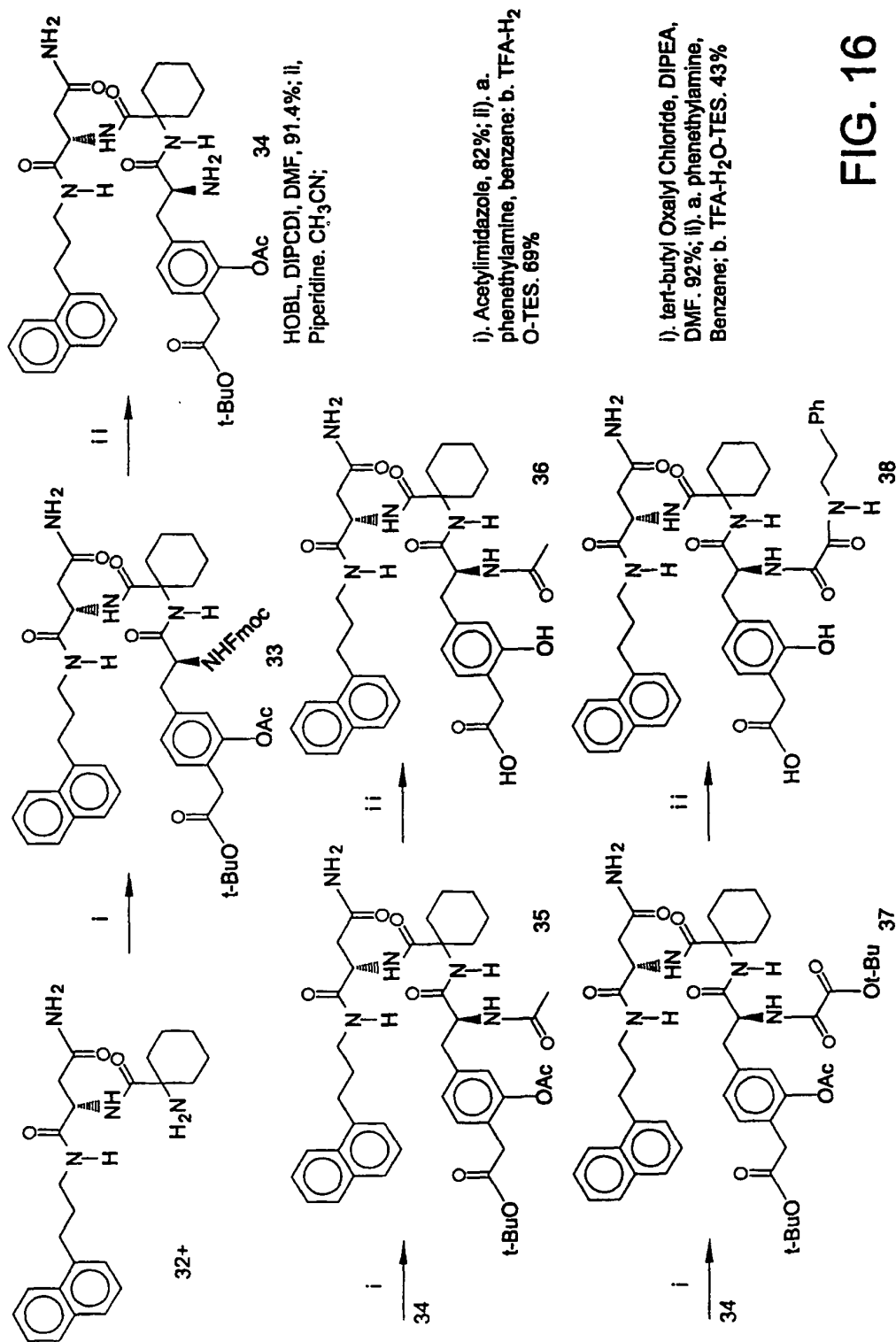


FIG. 16

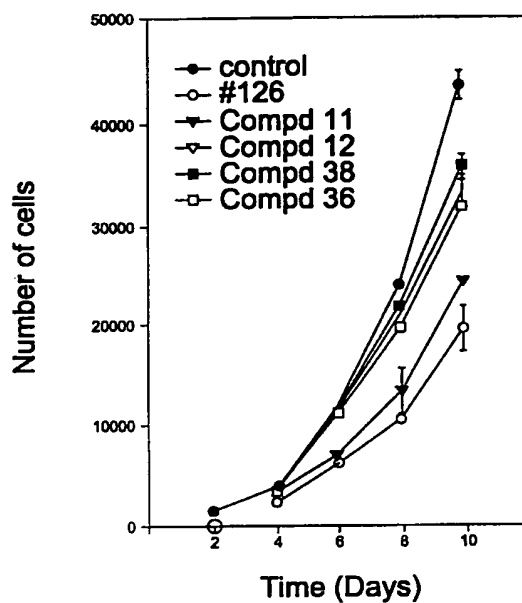


FIG. 17a

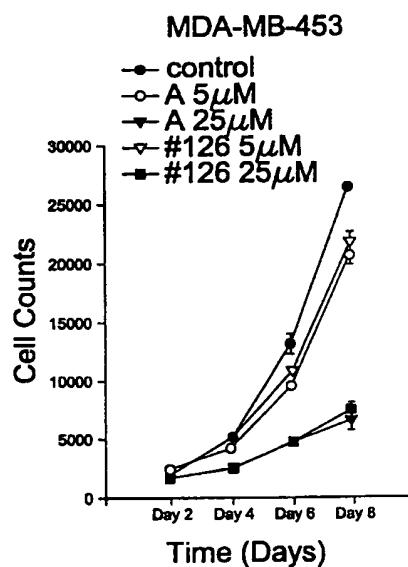


FIG. 17b

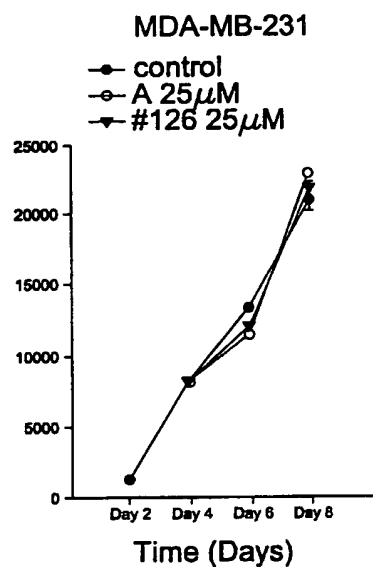
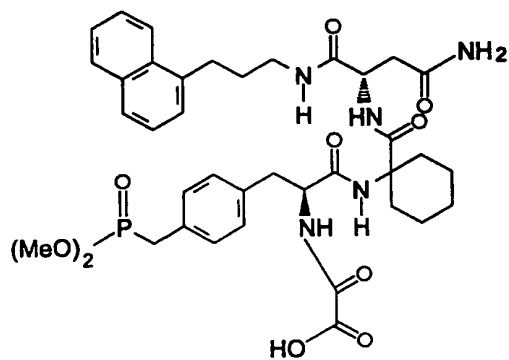
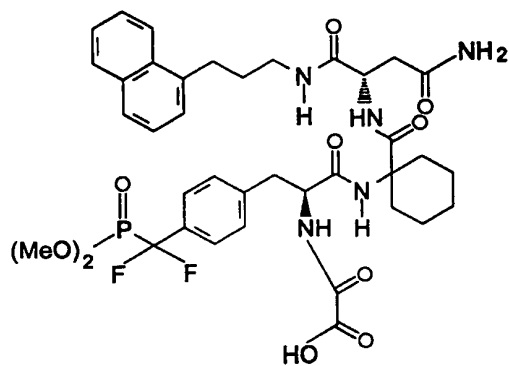


FIG. 17c

FIG. 18



Compd 126



Compd A

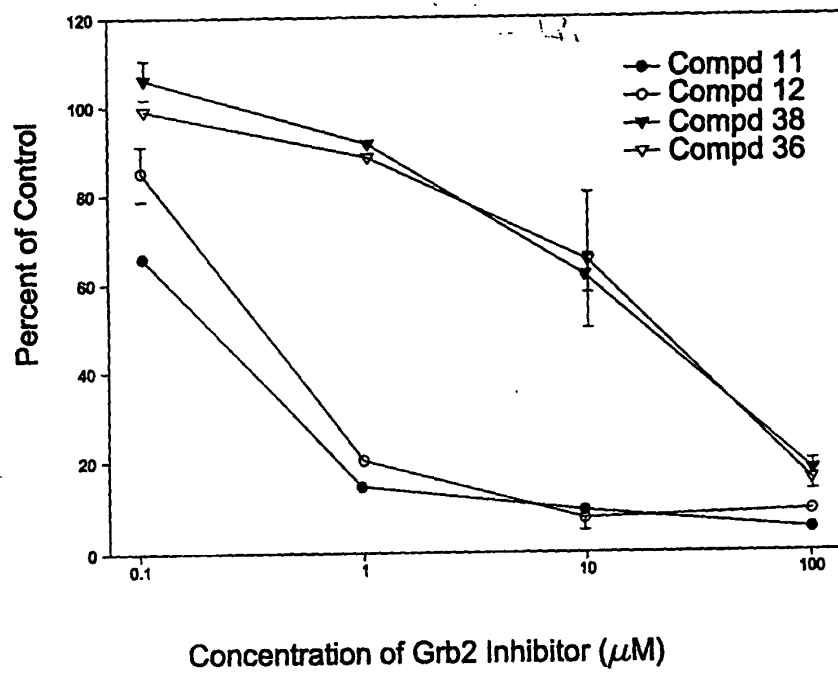


FIG. 19

209220-0572E650

**Synergistic Effect of Combination Treatment of
Grb2 Inhibitor with Chemotherapy Drugs**

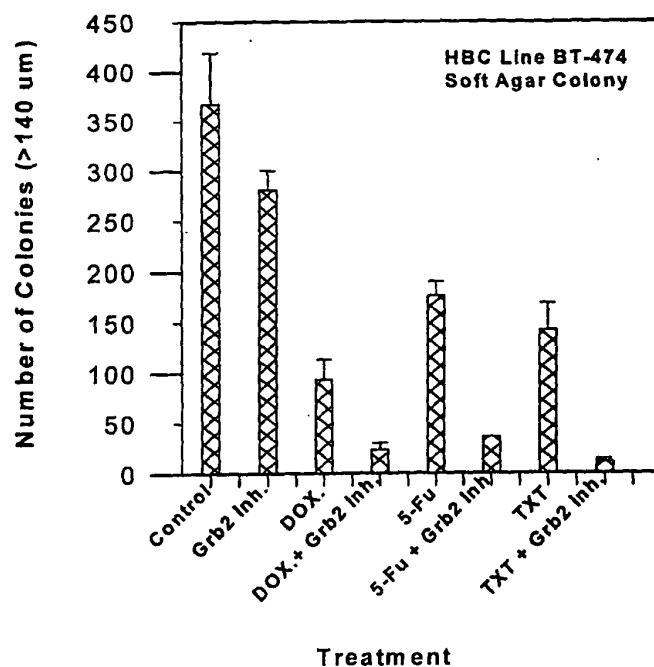


FIG. 20